AMENDMENTS

Amendments to the claims:

Please cancel claims 12-39 and 58-73 without prejudice or disclaimer and please enter new claims 74-128 as set forth in the complete listing of the claims that follows. This complete listing of the claims replaces previous claim listings.

1-73 (cancelled).

74 (new). A method for determining one or more sequence variations in a target nucleic acid, comprising:

(a) providing mass signals of fragments resulting from (i) specific cleavage of a target nucleic acid and a reference nucleic acid into fragments, and (ii) determining mass signals of the fragments;

(b) identifying differences in mass signals between target nucleic acid fragments and reference nucleic acid fragments, thereby identifying different fragments;

(c) generating one or more compomer witnesses corresponding to each different fragment identified in (b); and

(d) identifying a reduced set of candidate sequence variations corresponding to the compomer witnesses, whereby the one or more sequence variations in the target nucleic acid are determined from the candidate sequence variations.

75 (new). The method of claim 74, wherein the differences in mass signals in (b) are selected from the group consisting of missing signals, additional signals, signals that are different in intensity and signals having a different signal-to-noise ratio.

76 (new). The method of claim 74, wherein the mass signals are determined by mass spectrometry.

77 (new). The method of claim 74, wherein two or more sequence variations are determined.

78 (new). The method of claim 74, wherein the sequence variation is at one or more base positions.

79 (new). The method of claim 74, wherein the sequence variation is a mutation or a polymorphism.

80 (new). The method of claim 79, wherein the mutation is an insertion, a deletion or a substitution.

81 (new). The method of claim 74, wherein the polymorphism is a single nucleotide polymorphism.

82 (new). The method of claim 74, wherein the target nucleic acid is from an organism selected from the group consisting of eukaryotes, prokaryotes and viruses.

83 (new). The method of claim 86, wherein the organism is a bacterium.

84 (new). The method of claim 87, wherein the bacterium is selected from the group consisting of Helicobacter pyloris, Borelia burgdorferi, Legionella pneumophilia, Mycobacteria sp (e.g. M. tuberculosis, M. avium, M. intracellulare, M. kansaii, M. gordonae), Staphylococcus aureus, Neisseria gonorrheae, Neisseria meningitidis, Listeria monocytogenes, Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus sp., Streptococcus faecalis, Streptococcus bovis, Streptococcus pneumoniae, Campylobacter sp., Enterococcus sp., Haemophilus influenzae, Bacillus antracis, Corynebacterium diphtheriae, Corynebacterium sp., Erysipelothrix rhusiopathiae, Clostridium perfringens, Clostridium tetani, Enterobacter aerogenes, Klebsiella pneumoniae, Pasturella multocida, Bacteroides sp., Fusobacterium nucleatum, Streptobacillus moniliformis, Treponema pallidium, Treponema pertenue, Leptospira and Actinomyces israelli.

85 (new). The method of claim 74, which further comprises (i) providing a target nucleic acid and a reference nucleic acid; (ii) generating fragments of the target nucleic acid and the reference nucleic acid by specific cleavage; and (iii) determining mass signals of the fragments, wherein the mass signals of (iii) are provided in (a).

86 (new). The method of claim 85, wherein the target nucleic acid is in a mixture of nucleic acids.

87 (new). The method of claim 85, wherein the mixture comprises the reference nucleic acid.

88 (new). The method of claim 85, wherein the mixture comprises a plurality of reference nucleic acids.

89 (new). The method of claim 85, wherein the mixture comprises a plurality of target nucleic acids.

90 (new). The method of claim 85, wherein one specific cleavage agent is utilized to generate fragments.

91 (new). The method of claim 85, wherein two or more specific cleavage agents are utilized to generate fragments.

92 (new). The method of claim 85, wherein specific cleavage comprises treatment with an RNAse.

93 (new). The method of claim 85, wherein specific cleavage comprises treatment with a specific cleavage agent selected from the group consisting of RNase T1, RNase U2, the RNase PhyM, RNase A, chicken liver RNase (RNase CL3) and cusavitin.

94 (new). The method of claim 85, wherein specific cleavage comprises treatment with a glycosylase.

95 (new). The method of claim 85, wherein the target nucleic acid is in a pool of nucleic acids from individuals.

96 (new). The method of claim 85, wherein the target nucleic acid is genomic DNA from a single individual.

97 (new). The method of claim 85, wherein the target nucleic acid is selected from the group consisting of single stranded DNA, double stranded DNA, cDNA, single stranded RNA, double stranded RNA, DNA/RNA hybrid, PNA and a DNA/RNA mosaic nucleic acid.

98 (new). The method of claim 85, wherein the target nucleic acid is produced by transcription.

99 (new). The method of claim 85, wherein the mass signals are generated by mass spectrometry.

100 (new). The method of claim 74, wherein fragments are generated by simulated specific cleavage.

101 (new). The method of claim 74, wherein fragments of the reference nucleic acid are generated by simulated specific cleavage.

102 (new). The method of claim 74, wherein sequence variations in the target biomolecule permit genotyping a subject, forensic analysis, disease diagnosis or disease prognosis.

103 (new). The method of claim 74, wherein the method determines epigenetic changes in a target nucleic acid molecule relative to a reference nucleic acid molecule.

104 (new). The method of claim 74, wherein the target nucleic acid is from a tumor sample.

105 (new). The method of claim 76, wherein compomer witnesses are generated based upon parameters selected from the group consisting of mass of the different fragment, peak separation between fragments whose masses differ by a single nucleotide in type or length, and mass spectrometer resolution.

106 (new). The method of claim 74, wherein sequence variations in (d) are determined according to one or more reference sequences having at most k sequence variations.

107 (new). The method of claim 106, wherein k is one or two.

108 (new). The method of claim 106, wherein k is three or more.

109 (new). The method of claim 74, further comprising: (e) scoring the candidate sequence variations, whereby a sequence variation in the target nucleic acid is determined from the candidate sequence variation scoring in (e).

110 (new). The method of claim 109, wherein a simulated spectrum is generated for each sequence variation candidate, and each spectrum is scored.

111 (new). The method of claim 109, wherein scores assigned to a sequence variation candidate for multiple target nucleic acids are combined for an overall score of the sequence variation candidate.

112 (new). The method of claim 74, wherein sequence variation in the target nucleic acid is recorded in a record.

113 (new). The method of claim 74, wherein the one or more compomer witnesses for each different fragment have a mass within a mass difference from the actual mass of the different fragment.

114 (new). The method of claim 113, wherein the mass difference is the resolution of mass measurement.

115 (new). A method for detecting one or more sequence variations in a target nucleic acid, comprising:

(a) providing a plurality of fragmentation patterns resulting from (i) specific cleavage of a sample comprising a target nucleic acid by multiple cleavage reactions, wherein the target nucleic acid is in a nucleic acid mixture, and specific cleavage of a reference nucleic acid by the same cleavage reactions; and (ii) determining mass signals of the fragments;

(b) identifying differences in mass signals between the plurality of fragmentation patterns of target nucleic acid fragments and reference nucleic acid fragments, thereby identifying different fragments;

(c) identifying different fragments that are consistent with a particular sequence variation in the target nucleic acid;

(d) combining the consistent different fragments of (c) to obtain a spectrum of different fragments;

(e) generating from the spectrum of different fragments of (d) one or more compomer witnesses corresponding to each of the different fragments;

(f) determining sequence variations that are candidate sequences corresponding to the compomer witnesses;

(g) scoring the candidate sequences of (f); and

(h) determining one or more sequence variations in the target nucleic acid.

116 (new). The method of claim 115, wherein the mass signals are determined by mass spectrometry.

117 (new). The method of claim 115, wherein compomer witnesses are generated based upon parameters selected from the group consisting of mass of the different fragment, peak separation between fragments whose masses differ by a single nucleotide in type or length, and mass spectrometer resolution.

118 (new). The method of claim 115, wherein sequence variations in (f) are determined according to one or more reference sequences having at most k sequence variations.

119 (new). The method of claim 118, wherein k is one or two.

120 (new). The method of claim 118, wherein k is three or more.

121 (new). The method of claim 115, wherein one or more sequence variations are recorded in a record.

122 (new). The method of claim 115, wherein the one or more compomer witnesses for each different fragment have a mass within a mass difference from the actual mass of the different fragment.

123 (new). The method of claim 122, wherein the mass difference is the resolution of mass measurement.

124 (new). A method for detecting one or more sequence variations in a target nucleic acid, comprising:

(a) providing reference sequence *s*, a description of cleavage reaction conditions, whether modified nucleotides or amino acids are incorporated into all or part of the sequence, a list of signals corresponding to different fragments, and maximal sequence variation order k;

(b) generating a list of sequence variations that contain at most k insertions, deletions, and substitutions, and that have a different peak as a witness;

(c) computing bounded compomers (c[i,j],b[i,j]) in C.sub.k, and store the bounded compomers together with the indices i,j based on the reference sequence *s* and the specific cleavage reaction;

(d) identifying compomers for each different signal having a mass close to the signal mass by a sufficiently small mass difference, and store the compomers as compomer witnesses;

(e) for each compomer witness c', identifying bounded compomers (c,b) in C.sub.k, wherein D(c',c,b) is less than or equal to k;

(f) outputting sequence variations of *s* to a new reference sequence *s*' using at most k insertions, deletions, and substitutions for each bounded compomer (c,b) with indices i,j,

wherein:

a nucleotide is inserted or substituted at a cleaved base directly before position i if L is in b;

a nucleotide is inserted or substituted at a cleaved base directly after position j if R is in b;

at most k-#b insertions, deletions, and insertions are used that transform the fragment f=s[i,j] with corresponding compomer c into a fragment f' of s' with corresponding compomer c';

boundary b[i,j] of the substring s[i,j] or the corresponding compomer c[i,j] refers to a set of markers indicating whether cleavage of string *s* does not take place immediately outside the substring s[i,j];

marker L indicates s is not cleaved directly before i;

marker R, indicates *s* is not cleaved directly after j;

#b denotes the number of elements in the set b;

b[i,j] is a subset of the set {L,R} and denotes the boundary of s[i,j] as defined by the following:

b[i,j]:={L,R} if s is neither cleaved directly before i nor after j;

b[i,j]:={R} if s is cleaved directly before i, but not after j;

b[i,j]:={L} if s is cleaved directly after j, but not before i;

b[i,j]:={ } if s is cleaved directly before i and after j; and

#b[i,j] denotes the number of elements of the set b[i,j];

C.sub.k:={(c[i,j], b[i,j]):1.ltoreq.i.ltoreq.j.ltoreq.length of s, and ord[i,j]+#b[i,j].ltoreq.k};

ord[i,j] is the number of times the fragment s[i,j] is cleaved; and

D(c',c,b) is the distance between a compomer witness c' and a bounded compomer (c,b) and D(c',c,b):=d(c',c)+#b.

125 (new). The method of claim 124, wherein k is 1 or 2.

126 (new). The method of claim 124, wherein k is 3.

127 (new). The method of claim 124, wherein one or more sequence variations are recorded in a record.

128 (new). The method of claim 124, wherein the sufficiently small mass difference is the resolution of mass measurement.